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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/573,604	03/28/2006	Jo Klaveness	PN0369	6866

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EXAMINER	
SCHLIENTZ, LEAH H	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/573,604	KLAVENESS ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-22* is/are pending in the application.

4a) Of the above claim(s) *18 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-17,19,20 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement of Receipt

Applicant's Response, filed 4/13/2009, in reply to the Office Action mailed 12/11/2008, is acknowledged and has been entered. Claims 13-22 are pending, of which claims 18 and 21 have been withdrawn. Claims 13-17, 19, 20 and 22 have been amended. Claims 13-17, 19, 20 and 22 are examined herein on the merits for patentability.

Response to Arguments

Any rejection not reiterated herein has been withdrawn as being overcome by amendment. Response to Applicant's arguments is incorporated into rejection hereinbelow.

Double Patenting

Claims 13-17, 19, 20 and 22 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the claims of copending Application No. 10/573,606, 10/582,679, 10/582,680, 10/582,842, and 10/582,893, for reasons set forth in the previous Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-17, 19, 20 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for reasons set forth in the previous Office Action. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant argues on pages 5-6 of the Response that the amended claims are now limited to a method of optical imaging of endometriosis of an animate subject, and are no longer limited to a contrast agent per se. Applicant asserts that the specification provides sufficient information for a person skilled in the art to reproduce the method of amended claim 13. Applicant argues that the specification provides a description of suitable optical imaging techniques, plus a description of targeting molecules, and methods of labelling them with optical reporters. Applicant argues that the person skilled in the art can either use the contrast agents described in the specification or generate new ones, and assert that the claim scope should not be limited by the possible advent of new targeting molecules. Applicant contends that if a person skilled in the art has available a compound with an affinity for one of the targets described, then labelling such a compound with an optical reporter is taught by the present specification.

This is not found to be persuasive. In order to practice the claimed method, one would necessarily be in possession of the contrast agent, thus a reasonable description of the contrast agent which are used to practice the method is necessary. While Applicant has provided a description of a few specific vectors (i.e. RGD-type vector for integrins; progesterone as a vector for progesterone receptor, estrogen as a vector for extrogen receptor, folate for folate binding proteins (pages 12-13 and Examples). Such a limited disclosure of a single vector for a few receptors which are associated with endometriosis does not provide sufficient description to show that Applicant was in possession of the full scope of a contrast agent comprising an optical imaging moiety and any vectors (e.g. any small molecule, any peptide, any oligonucleotide, any antibody etc) which may target any receptor which is associated with endometriosis. With regard to Applicant's argument that the claim scope should not be limited by the possible future advent of new targeting molecules, and that if a person skilled in the art has available a compound with affinity for one of the targets described, then labeling such a compound with an optical reporter is taught by the specification, this is not found to be persuasive because the specification has not provided a clear description of the full scope of targeting vectors which were envisaged at the time the specification was filed. Future-developed targeting moieties would not be encompassed by vectors that Applicant was in possession of at the time the application was filed, especially since Applicant has only described a single vector for each target/receptor.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 13-17, 19, 20 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weissleder (US 2003/0044353) in view of Schneider (US 6,387,629), for reasons set forth in the previous Office Action.

Applicant argues on pages 8-10 of the Response that Schneider already discloses in vivo imaging of endometriosis in a subject, and that the disclosure of Schneider in that regard (in vivo imaging of endometriosis) is limited to laparoscopy. Applicant asserts that in the context of in vivo optical imaging, Schneider teaches local administration to the site of disease/lesion, and that present claim 1 is amended to specify intravenous administration. Applicant contends that the combination of Weissleder + Schneider is believed to be an invalid combination, and that Schneider's teaching of in vivo imaging but using laparoscopy techniques and administration at the lesion site. Applicant argues that the combination suggested by the Examiner contradicts the teaching of Schneider itself. Applicant further argues that Schneider's teaching of radioisotope or MRI label as being preferred teaches away from a fluorescent label as a probe.

This is not found to be persuasive. Weissleder teaches intravenous administration of his probes and methods of in vivo optical imaging in the NIRF range (see paragraph 0129 and Examples). Schneider is relied upon not for specific imaging procedure, but for the teaching that cathepsin s expression is up-regulated in

endometriotic tissue and that cathepsin s gene product can be labeled with fluorescent probe. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Regarding Applicant's argument that Schneider teaches radioisotope or MRI label are preferred, see MPEP 2123 (1). Patents are relevant as prior art for all they contain. "The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." *In re Heck*, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting *In re Lemelson*, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968)). A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied,* 493 U.S. 975 (1989). See also >*Upsher-Smith Labs. v. Pamlab, LLC*, 412 F.3d 1319, 1323, 75 USPQ2d 1213, 1215 (Fed. Cir. 2005).

New Grounds for Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 13-17, 19, 20 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith *et al.* (US 2004/0053823) in view of Weissleder *et al.* (US 2003/0044353).

Smith discloses isolated MMP-2, MMP-9 and MT1-MMP selective substrate polypeptides or functional peptidomimetics. The selective substrate polypeptides contain the following sequences: MMP-2 selective substrate polypeptides contain SEQ ID NOS:1-27, MMP-9 selective substrate polypeptides contain SEQ ID NOS:28-35, and MT1-MMP selective substrate polypeptide contain SEQ ID NOS:36-40. In addition, the invention provides a method of preferentially directing a moiety to a site of MMP-2 activity by administering to a subject an effective amount of an isolated MMP-2 selective substrate polypeptide containing SEQ ID NOS:45-47 linked to a moiety (abstract). Methods of preferentially directing a moiety to a site of MT1-MMP, MMP-2, or MMP-9 activity by administering to a subject an isolated MT1-MMP, MMP-2, or MMP-9 selective substrate polypeptide linked to a moiety. The methods of the invention can be useful in diagnosing or treating diseases where these metalloproteinases are involved which include, for example, cancer or other disorders involving pathogenic angiogenesis. Disorders involving pathogenic angiogenesis include, for example, diseases of ocular neovacularization, arthritis, atherosclerosis, endometriosis, and skin diseases (paragraph 0014). A moiety can be a diagnostic agent such as a radioactive or fluorescent agent (paragraph 0078). A diagnostic moiety can also be linked to a selective substrate polypeptide of the invention in an

inactive form. This type of diagnostic moiety would be targeted to a site of metalloproteinase activity where it would be activated. For example, a fluorescent probe such as a near-infrared fluorescence (NIRF) imaging probe can be in an inactive or quenched state until it reaches a desired site where it can be converted to an active or un-quenched state (paragraph 0079). A diagnostic moiety can also be, for example, a MRI contrast dye or a fluorescent agent. In one embodiment, the invention provides an isolated MT1-MMP, MMP-2, or MMP-9 selective substrate polypeptide of the invention described above where the diagnostic moiety is a quenched fluorophore, for example, a near-infrared fluorescence (NIRF) imaging probe. These biocompatible, optically quenched NIRF imaging probes can generate a strong NIRF signal after enzyme activation such as hydrolysis by a proteinase. A NIRF imaging probe can be linked to a MT1-MMP, MMP-2, or MMP-9 selective substrate polypeptide of the invention in order to specifically target the NIRF imaging probe to a site of activity of these MMPs such as a tumor or a site of inflammation. The NIRF moiety linked to a selective substrate polypeptide of the invention can be used to define and measure a site of MMP activity, for example, this conjugate can be used to image a tumor (paragraph 0088). The methods of the invention also can be useful for preferentially directing a moiety to angiogenic vasculature that is not tumor vasculature or associated with neoplastic disease. Angiogenesis within the female reproductive tract, for example, is critical for normal reproduction and can be involved in pathogenesis of endometriosis. Thus, a method of the invention can be useful in preferentially directing a moiety to non-tumor angiogenic vasculature such as endometrial vasculature.

Smith does not specifically recite the absorption range of his fluorescent probe used in directing a moiety to angiogenic vasculature, such as endometriosis, but teaches that NIRF probes are desirable.

Weissleder discloses imaging probes that have altered optical properties after interaction with a target molecule, i.e., activation of the probe. This enables 1) detection of early disease, 2) a high target/background ratio for improved detection of subtle disease, and 3) non-invasive, imaging of internal molecular targets based on their biological activity (paragraph 0007). A "chromophore" includes, but is not limited to, a fluorochrome, non-fluorochrome chromophore, fluorescence quencher, or absorption chromophore, including but not limited to organic and inorganic fluorochromes (paragraph 0012). A "targeting moiety" is a moiety bound covalently or noncovalently to a probe, which moiety enhances the concentration of the probe in a target tissue relative to surrounding tissue (paragraph 0018). Chromophores useful in the new probes include near infrared chromophores such as Cy5.5, Cy5, Cy7, IRD41, IRD700, NIR-1, IC5-OSu, LaJolla Blue, Alexaflour 660, Alexflour 680, FAR-Blue, FAR-Green One, FAR-Green Two, ADS 790-NS, ADS 821-NS, indocyanine green (ICG) and analogs thereof, indotricarbocyanine (ITC), etc. (paragraph 0045). Imaging probes with excitation and emission wavelengths in the near infrared spectrum are preferred, i.e., 650-1300 nm. Use of this portion of the electromagnetic spectrum maximizes tissue penetration and minimizes absorption by physiologically abundant absorbers such as hemoglobin and water. Ideal near infrared chromophores for in vivo use exhibit the following characteristics: (1) narrow spectral characteristics, (2) high sensitivity

(quantum yield), (3) biocompatibility, and (4) decoupled absorption and excitation spectra (paragraph 0062). Intravenous administration is disclosed (paragraph 0129). Weissleder teaches that several MMPs are expressed in cancers at much higher levels than in normal tissue and the extent of expression has been shown to be related to tumor stage, invasiveness, metastasis, and angiogenesis (paragraph 0071). Compositions and methods for recording native enzyme activities in tumors. This represents an invaluable in vivo tool for elucidation of the functional contribution of specific agents in tumorigenesis, metastagenesis and angiogenesis. Indeed, such measurements can be performed at different resolutions ranging from the microscopic cellular level (e.g., using intravital, confocal, or two photon microscopy) to the macroscopic whole tumoral level (e.g., near infrared diffuse optical tomography, phase array detection, or reflectance imaging). The methods of the present invention may also be used to image dose responses (paragraphs 0197-8).

It would have been obvious to one of ordinary skill in the art to provide a NIRF probe such as a cyanine dye on the peptides of Smith for imaging of endometriosis. One would have been motivated to so because Smith teaches that NIRF probes are suitable for labeling his peptides and use thereof in optical imaging. One would have had a reasonable expectation of success in doing so because Weissleder teaches the benefits of NIRF probes such as (1) narrow spectral characteristics, (2) high sensitivity (quantum yield), (3) biocompatibility, and (4) decoupled absorption and excitation spectra. Both Smith and Weissleder are directed to NIRF labeling of MMP peptide substrates for targeting angiogenesis, and Smith teaches that angiogenesis within the

female reproductive tract is critical for normal reproduction and can be involved in pathogenesis of endometriosis and that his compounds can be useful in preferentially directing a moiety to non-tumor angiogenic vasculature such as endometrial vasculature.

Claims 13-17, 19, 20 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fevig *et al.* (*J. Med. Chem.*, 1987, 30, p. 156-165) in view of Wallace *et al.* (US 6,096,874), further in view of Weissleder (US 2003/0044353).

Fevig discloses thioether-linked norhexestrol-fluorophore conjugates as shown in Table III, having high estrogen receptor binding affinity and favorable fluorescence quantum yield. The compounds are intended for use in optical imaging of tumor, e.g. such as in breast cancer (see page 156, Table III, page 162).

Fevig does not specifically recite imaging of endometriosis with the compounds, and does not teach flurophores having absorption maximum in the range of 600 to 1300 nm.

However, in addition to breast cancer, estrogen receptor-rich tissues may also be be found in breast, ovarian, uterine and brain tissue.

For example, Wallace teaches tamoxifen derivatives having a tamoxifen derivative conjugated to a DTPA diagnostic moiety. The compounds are used as highly specific imaging agents for estrogen-receptor rich tissues (abstract). They may be used in imaging of estrogen receptors, for example in breast, ovarian, uterine and brain

tissues and may therefore be useful in the diagnosis of estrogen receptor positive cancers, meningiomas and endometriosis.

Weissleder discloses imaging probes that have altered optical properties after interaction with a target molecule, i.e., activation of the probe. This enables 1) detection of early disease, 2) a high target/background ratio for improved detection of subtle disease, and 3) non-invasive, imaging of internal molecular targets based on their biological activity (paragraph 0007). A "chromophore" includes, but is not limited to, a fluorochrome, non-fluorochrome chromophore, fluorescence quencher, or absorption chromophore, including but not limited to organic and inorganic fluorochromes (paragraph 0012). A "targeting moiety" is a moiety bound covalently or noncovalently to a probe, which moiety enhances the concentration of the probe in a target tissue relative to surrounding tissue (paragraph 0018). Chromophores useful in the new probes include near infrared chromophores such as Cy5.5, Cy5, Cy7, IRD41, IRD700, NIR-1, IC5-OSu, LaJolla Blue, Alexaflour 660, Alexflour 680, FAR-Blue, FAR-Green One, FAR-Green Two, ADS 790-NS, ADS 821-NS, indocyanine green (ICG) and analogs thereof, indotricarbocyanine (ITC), etc. (paragraph 0045). Imaging probes with excitation and emission wavelengths in the near infrared spectrum are preferred, i.e., 650-1300 nm. Use of this portion of the electromagnetic spectrum maximizes tissue penetration and minimizes absorption by physiologically abundant absorbers such as hemoglobin and water. Ideal near infrared chromophores for in vivo use exhibit the following characteristics: (1) narrow spectral characteristics, (2) high sensitivity

(quantum yield), (3) biocompatibility, and (4) decoupled absorption and excitation spectra (paragraph 0062). Intravenous administration is disclosed (paragraph 0129).

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide the compounds of Fevig for imaging of additional tumor tissues in addition to breast tumor, such as endometriosis, when the disclosure of Fevig is taken in view of Wallace. Both Fevig and Wallace are directed to diagnostic imaging of tumor or cancer using diagnostic moieties conjugated to targeting agents directed to estrogen receptor. Since Wallace teaches that estrogen receptor rich tissues include both both breast and uterine tissue, and teaches that compounds having affinity for estrogen receptor may be useful for imaging estrogen receptor positive cancers, such as endometriosis, one would have had a reasonable expectation of success in using Fevig's compounds having high affinity for estrogen receptor for imaging endometriosis. It would have been further obvious to substitute one functionally equivalent optical imaging moiety for another in the compounds of Fevig, such as those disclosed by Weissleder. One would have been motivated to do so because Weissleder teaches that targeted chromophores having and emission wavelengths in the near infrared spectrum are preferred, i.e., 650-1300 nm have benefits such as (1) narrow spectral characteristics, (2) high sensitivity (quantum yield), (3) biocompatibility, and (4) decoupled absorption and excitation spectra (paragraph 0062).

Conclusion

No claims are allowed at this time.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS